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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/648,863 | 08/26/2003 | John A. Delyani | C-3258 | 3765 |

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| EXAMINER | |
|---|---|
| HUI, SAN MING R | |
| ART UNIT | PAPER NUMBER |
| 1617 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 02/08/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/648,863 | DELYANI ET AL. | |
| | Examiner | Art Unit | |
| | San-ming Hui | 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-74* is/are pending in the application.

4a) Of the above claim(s) *1-26,38-52,54-63 and 68-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-37,53 and 64-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

This is a continuation application of US Serial 09/709253, filed 11/8/2000.

Claims 1-74 are pending.

### *Election/Restrictions*

Applicant's election with traverse of the invention of Group II, claims 27-37, 53, 57, 61, and 64-67, and the specie of eplerenone, in the reply filed on November 10, 2006 is acknowledged. The traversal is on the ground(s) that no undue burden should be presented since search for all the claims are directed to a method of treatment, inhibition or prevention comprising the administration of an aldosterone antagonist. This is not found persuasive because the method of treatment, inhibition or prevention for various diseases or conditions is actually claimed herein. The inventions herein function differently. Note that the search fields for materially different methods of use employing a composition containing the same or different ingredients are diverse. Each method relates to a separate field of medical technology e.g., treat, prevent, and inhibit pathogenic changes of an artery; treating, preventing or inhibiting restenosis of an artery resulting from vascular injury; treating, preventing or inhibiting vascular constrictive remodeling resulting from vascular injury; and treating, preventing or inhibiting vascular collagen accumulation resulting from vascular injury having a separate field of search. Each composition contains different active ingredients classified in different classifications, which are recognized as separate fields of art. The search is not limited to patent files. Therefore, the search for the methods encompassed by the claims presents an undue burden to the Office.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-26, 38-52, 54-56, 58-60, 62-63, 68-74 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on November 10, 2006.

Claims 57 and 61 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on November 10, 2006.

Claims 27-37, 53, and 64-67 are examined to the extent they read on the elected invention and species.

## *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-37, 53, and 64-67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In the instant case, the specification does not provide sufficient

information and guidance so that one of skilled in the art would practice the herein claimed invention without undue experimentation.

*Ex parte Forman* (230 USPQ 546, BdPatApp & Int.) and *In re Wands* (858 F.2d 731, 8 USPQ2d 1400, 1404, Fed. Cir. 1988) provide several factors in determining whether the specification of an application allows the skilled artisan to practice the invention without undue experimentation. Having said factors in mind, the instant specification fails to reasonably provide enablement for methods of preventing the claimed condition. Specifically, the recitation of "prevention of restenosis" in the instant claims, directs the claims to methods of preventing a pathological condition. However, the specification fails to properly enable such methods.

In the instant case, the burden of enabling for preventing restenosis requires appropriate screening testing, subsequent data compilation, and finally appropriate data analysis, to assess and properly enable one skill in the art whether restenosis are prevented from formation in a patient. For example, the specification must provide adequate guidance whether restenosis can be prevented from forming in a patient once the composition is administered to a subject susceptible to develop restenosis.

Moreover, the specification must provide direct evidence associating the claimed prevention to the composition applied. The burden of showing preventative properties is greater than that of enabling a treatment, because one of ordinary skill in the art must not only show competent screening of those subjects susceptible to such conditions, but also show that the efficacy of a preventative method is directly caused by applying or administering the instantly claimed composition to the susceptible subjects.

In this case, there are no teachings for screening methods identifying susceptible subjects nor is there any direct evidence of efficacy establishing a preventative property associated with the claimed composition. Furthermore, the state of the prior art concerning methods of preventing restenosis formation is not well described, nor does it provide for any absolute prevention. Accordingly, undue experimentation is necessary to determine screening and testing protocols to demonstrate the efficacy of the presently claimed invention.

The instant specification does not provide any working examples nor does it describe the in vivo correlation between smooth muscle cells and the aldosterone levels. Accordingly, in order to practice the claimed invention commensurate in scope with the claims, one of ordinary skill in the art must perform undue experimentation to screen for susceptible mammals, test and demonstrate the efficacy of the compositions for preventative methods. Accordingly, specification does not provide adequate enablement under 35 U.S.C. 112, first paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 29 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "substantially" recited in claim 29 is a relative term which renders the claims indefinite. The term "substantially" is not defined by the claim, the specification

does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what the degree of surgery and trauma would result in the herein claimed vascular injury.

The rejection set forth below is directed to the treatment of restenosis.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 27-37, 53, and 64-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baim and Grossman (Harrison's Principles of Internal Medicine, 13th ed., 1994, page 986-987) in view of Delyani(A) (European Heart Journal, Aug. 1999, vol. 20, suppl, p.613) and Delyani(B) (Expert. Opin. Invest. Drugs, 1998;7(5):753-759), all of the references of record in the parent application.

Baim and Grossman teaches the angioplasty procedure involves local dissection, which could results in rapid closure of the already dilated blood vessels soon after the withdrawal of the balloon catheter. Because of this, vasodilators and anticoagulants are used routinely in order to prevent abrupt closure due to spasm and/or thrombus formation (see page 986, col. 2, second paragraph). Baim and Grossman also teaches that when recurrent ischemia develops more than 6 months after angioplasty, it usually reflects progression of disease at another site, rather than restenosis (See page 986, col. 2, last paragraph).

The reference does not teach the employment of eplerenone to treat or inhibit pathogenic changes in the blood vessels result from the angioplasty procedure. The reference does not expressly teach the site of the injury occurring in the pulmonary artery. The reference does not expressly teach the vascular injury has the gap angle of at least 10 degree. The reference does not expressly teach the pathogenic changes is lumental narrowing, restrictive neointima formation, or migration and proliferation of smooth muscle cells. The reference does not expressly teach the ratio of intima area, to vessel area, for the artery site of maximal injury as below 0.37, or below 0.30. The reference does not expressly teach the eplerenone regimen as the administration of eplerenone for at least 6 months after the vascular injury. The reference does not expressly teach the dosage of eplerenone to be 15mg/kg or less.

Delyani (A) teaches eplerenone, in a dosage of 300mg/kg/day, as useful to attenuate cardiac maladaptive reactive fibrosis and left ventricular remodeling (pathogenic changes) 3 days after a vascular injury, myocardial infarction (see the

abstract). Delyani (A) also teaches eplerenone as useful to lower the collagen volume in noninfarcted area (See the abstract).

Delyani (B) also teaches aldosterone antagonist attenuates the cardia fibrosis of cardiomyopathic hamsters (See page 755, col. 1, second paragraph). Delyani (B) teaches anti-aldosterone agent is useful in inhibiting vasoconstriction due to the defect in hyperaldosteronism (See page 755m col. 2, first paragraph). Delyani (B) also teaches eplerenone has antifibrotic effects in animals comparable to the antifibrotic effects of spironolactone (See page 757, col. 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ eplerenone, at the claimed administered dosage and regimen herein, in a method to treat pathogenic changes, such as lumental narrowing, restrictive neointima formation, and migration and proliferation of smooth muscle cells, resulting from angioplasty or surgery. Examiner notes that lumental narrowing, restrictive neointima formation, and migration and proliferation of smooth muscle cells are all causing restenosis (narrowing of the blood vessels). It would have been obvious to one of ordinary skill in the art at the time the invention was made to treat pathogenic changes by administering eplerenone to the pulmonary artery, for treating the injury site ratio of intimal area to vessel area at the artery site of maximal injury to be below 0.37, or below 0.30, and/or the vascular injury has the gap angle of at least 10 degrees.

One of ordinary skill in the art would have been motivated to employ eplerenone, in a dosage and regimen herein, in a method to treat pathogenic changes, such as lumental narrowing, restrictive neointima formation, and migration and proliferation of

smooth muscle cells, caused by angioplasty or surgery. Eplerenone is known to be useful to inhibit fibrotic and collagen formation, which would be therefore reasonably expected to be treating pathogenic changes such as lumental narrowing, restrictive neointima formation, vascular collagen formation and migration and proliferation of smooth muscle cells. Please note that vasodilators are routinely administered to patient received angioplasty in order to prevent the rapid closure of the blood vessel (pathogenic changes). Eplerenone is a known vasoconstriction-inhibiting agent. Its anti-vasoconstrictive effect would have been reasonably expected to be useful in preventing the narrowing of the blood vessel. In addition, its anti-fibrotic effect in other area would have been reasonably expected to be useful in prevent further ischemic damage to the blood vessels in other area after angioplasty since sometimes ischemia is observed even after 6 months of angioplasty. Furthermore, optimization of therapeutic effect parameters (e.g., dosage range and dosing regimens) is obvious as being within the skill of the artisan.

One of ordinary skill in the art would have been motivated to administer eplerenone to pulmonary artery, where in the injury site ratio of intimal area to vessel area at the artery site of maximal injury to be below 0.37, or below 0.30, and/or the vascular injury has the gap angle of at least 10 degree. This motivation results from the cited prior art teaching that eplerenone is effective to inhibit vasoconstriction and fibrotic formation, which thereby treating and inhibit further narrowing of the blood vessels after angioplasty procedure. Therefore, employing eplerenone having been reasonably expected to be useful regardless of the conditions (various injury site ratio and gap

angle) and location (coronary arteries vs. pulmonary arteries) of the injury sites since eplerenone is known to attenuate collagen volume and fibrotic effect; thus, treating the pathogenic changes thereby, as discussed above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (571) 272-0626. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

San-ming Hui
Primary Examiner
Art Unit 1617